Cerebral Blood Flow Methodology

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1. Kinetics of Diffusible Flow Tracers

The tissue concentration $C_t(t)$ of a perfectly diffusible tracer in response to an arterial input $C_a(t)$ is given by the general expression (Ohta 1996):

$$C_t(t) = (1 - V_0) \cdot K_1 \cdot \int_0^t C_a(\tau) e^{-k_2(t-\tau)} d\tau + V_0 \cdot C_a(t) \quad (1)$$

K_1 is the unidirectional clearance of tracer, assumed to be equal to CBF for freely diffusible substances such as water and Xenon. $k_2 = \frac{K_1}{V_d}$, where V_d is the distribution volume of the tracer.

V_0 is the vascular distribution volume for the tracer in the tissue. In bolus type experiments such as $H_2{}^{15}O$ PET, this term is significant, whereas for inhalation of Xenon, the vascular term is not generally included, and $V_o = 0$. To measure CBF, the free parameters in Eq 1 are varied to obtain an optimal fit of the expression to regional uptake curves, using non-linear, least squared regression analysis.

2. Effects of Pathophysiology on Kinetic Parameters

All three kinetic parameters in Eq. 1 are affected by elements inherent to the pathophysiology of brain disease where vascular permeability, tissue water content or vascular distribution volume are altered, e.g. brain tumors

2.1. K_1

In practice, the passage of tracer molecules from blood to tissue is to some extent limited by the blood brain barrier (BBB). The diffusion capacity of the BBB is often described by the permeability (P) of the BBB to the molecule multiplied by the capillary surface area (S) available for diffusion. If the passage of a tracer molecule across the BBB is significantly limited, the K_1 determined from (1) underestimates flow. The degree of underestimation is dependent on the magnitude of PS (Crone 1963; Renkin 1959):

$$K_1 = CBF \cdot \left(1 - e^{-\frac{PS}{CBF}}\right) \quad (2)$$

For small flow rates and large PS values, the clearance of a tracer molecule is hence mainly restricted by flow, whereas for increasing flow or lower PS, diffusion across the BBB becomes limiting. Several substances alter capillary water permeability, eg. blucocoticoids (GC). Assuming the PS product of water to be roughly 100ml/100ml/min, and the PS decrease to 40% (Reid 1983) in response to GC treatment, without any concomitant change in CBF, the clearance of water would decrease:

$$\frac{K_1^{dex}}{K_1} = 1 - e^{-\frac{60}{50}} \Big/ 1 - e^{-\frac{100}{50}} = 0.699 / 0.865 = 0.81$$

Therefore, assuming $K_{1,w}$=CBF, one would detect an apparent decrease in CBF of 20% solely due to a decrease in PS of cerebral capillaries. The exact value of PS and its relation to CBF is, however, poorly understood.

2.2.V_d

Brain edema is often significant in cerebral pathology, causing the tissue fraction to be significantly decreased. For CBF measurements, the presence of edema may pose a problem. For techniques assuming a fixed distribution volume of the applied tracer will hence (i) *underestimate* flow in edema zone for water soluble tracers and (ii) *overestimate* flow using lipid-soluble tracers. More importantly, monitoring the effects on CBF of a drug that selectively decreases edema would show an *increase* in estimated flow for a lipid-soluble tracer simply due to the increase in distribution volume.

2.3. V_o

In early PET (And ASL) studies, the contribution of the vascular signal was largely ignored, causing some bias due to a fast tissue component that could be misinterpreted as a fast flow rate.

3 Bolus Tracking.

3.1. Cerebral Blood Volume Measurements

The vascular volume fraction can be assessed by dynamically imaging the passage of an intravascular tracer, so-called *bolus tracking*. By detecting the arterial as well as the total tissue concentration as a function of time during a single transit, the CBV can be determined from the ratio of the areas under the tissue and arterial concentration time curves, respectively (Stewart 1894; Meier and Zierler 1954; Zierler 1965; Zierler 1962).

$$CBV = \frac{\int_{-\infty}^{\infty} C_t(\tau)d\tau}{\int_{-\infty}^{\infty} C_a(\tau)d\tau} \qquad (3)$$

In MR experiments, arterial measurements are not readily quantifiable, and relative measurements are therefore often used by simply integrating the area under the concentration time curve (Rosen *et al.* 1990; 1991a; 1991b).

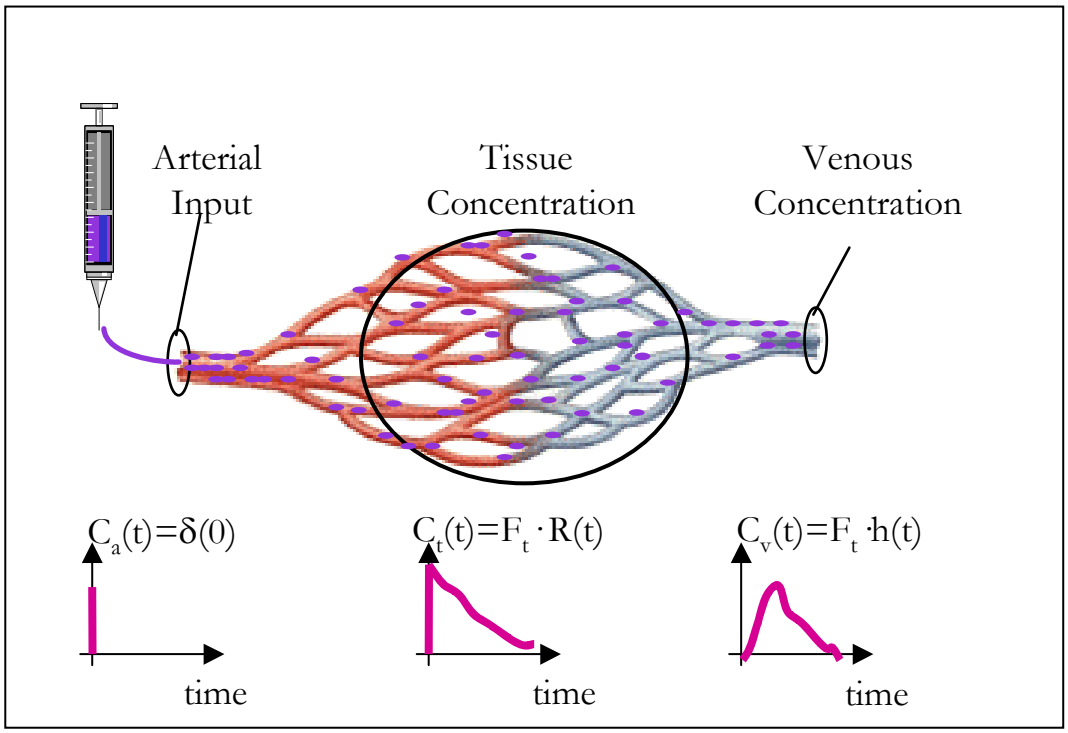

Figure 1

Idealized, infinitely sharp bolus injection into the bloodstream of a schematic tissue volume. The tissue concentration as a function of time is in this case given by the flow multiplied by the residue function R(t). Notice R(0)=1 and R(∞)=0. The tracer concentration in the vein is determined by the transport function, h(t). The latter is given by the time derivative of R(t): h(t)=-R´(t). In actual experiments, the bolus reaching the brain will have a finite duration. The tissue concentration time curve becomes a convolved signal of the impulse response above (i.e. $F_t \cdot R(t)$) with the arterial input shape (Eq. 4).

3.2. Cerebral Blood Flow

Figure 1.a. shows a schematic vascular residue. An infinitely sharp input is injected into the blood stream of a tissue element. The tracer follows the bloodstream through arterioles, capillaries, venules, to finally leave the tissue vasculature through the vein. The *residue function* describes the fraction of injected tracer particles still present in the vasculature at a given time after an instantaneous, infinitely sharp bolus injection into the feeding vessel. The area of the residue function is the average time spent by tracer molecules in the vasculature, the *mean transit time*, MTT.

In real experiments, the arterial input function becomes dispersed during its passage from the venous injection site to the brain. Consequently, the tissue concentration becomes a convolution of the residue function with the finite, arterial input function. This leads to the operational equation (Meier and Zierler 1954; Zierler 1965; Zierler 1962; Axel 1980):

$$C_t(t) = F_t \cdot C_a(t) \otimes R(t) \qquad (4)$$

where F_t is tissue flow and R(t) is the residue function. The symbol $\otimes$ denotes convolution, taking into account that the arterial input $C_a(t)$ has a finite duration. The majority of the theoretical work presented in this ISMRM course deals with models and mathematical procedures to find F_t from MRI measurements of arterial and tissue tracer levels.

Literature

Crone C. 1963 The permeability of capillaries in various organs as determined by use of the indicator diffusion method. Acta Physiol.Scand. 58:292-305.

Meier P, Zierler KL. 1954. On the Theory of the Indicator-Dilution Method for Measurement of Blood Flow and Volume. J.Appl.Phys. 6:731-44.

Ohta S, Meyer E, Fujita H, Reutens DC, Evans A, Gjedde A. 1996 Sep. Cerebral [15O]water clearance in humans determined by PET: I. Theory and normal values. J Cereb.Blood Flow Metab. 16(5):765-80.

Reid AC, Teasdale GM, McCulloch J. 1983 Jan. The effects of dexamethasone administration and withdrawal on water permeability across the blood-brain barrier. Ann Neurol 13(1):28-31.

Renkin EM. 1959. Exchangeability of tissue potassium in skeletal muscle. Am.J Physiol. 197:1211-5.

Rosen BR, Belliveau JW, Aronen HJ, Kennedy D, Buchbinder BR, Fischman A, Gruber M, Glas J, Weisskoff RM , Cohen MS, and others. 1991 Deca. Susceptibility contrast imaging of cerebral blood volume: human experience. Magn.Reson.Med. 22(2):293-9.

Rosen BR, Belliveau JW, Buchbinder BR, McKinstry RC, Porkka LM, Kennedy DN, Neuder MS, Fisel CR, Aronen HJ, Kwong KK, and others. 1991 Junb. Contrast agents and cerebral hemodynamics. Magn.Reson.Med. 19(2):285-92.

Rosen BR, Belliveau JW, Vevea JM, Brady TJ. 1990 May. Perfusion imaging with NMR contrast agents. Magn.Reson.Med. 14(2):249-65.

Stewart GN. 1894 Nov 11. Researches on the circulation time in organs and on the influences which affect it. Parts I-III. Journal of Physiology (London) 15:1-89.

Villringer A, Rosen BR, Belliveau JW, Ackerman JL, Lauffer RB, Buxton RB, Chao YS, Wedeen VJ, Brady TJ. 1988 Feb. Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. Magn.Reson.Med. 6(2):164-74.

Weisskoff RM, Zuo CS, Boxerman JL, Rosen BR. 1994 Junb. Microscopic susceptibility variation and transverse relaxation: theory and experiment. Magn.Reson.Med. 31(6):601-10.

Zierler KL 1962 Theoretical Basis of Indicator-Dilution Methods for Measuring Flow and Volume. Circ.Res.10:393-407.

Zierler KL 1965. Equations for Measuring Blood Flow by External Monitoring of Radioisotopes. Circ.Res. 16:309-21.